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<p>(21) International Application Number: <b>PCT/IB95/00279</b></p> <p>(22) International Filing Date: <b>20 April 1995 (20.04.95)</b></p> <p>(71) Applicant (<i>for all designated States except US</i>): <b>PFIZER INC.</b> [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): <b>PISCOPIO, Anthony, D.</b> [US/US]; 196 Payer Lane, Mystic, CT 06355 (US). <b>RIZZI, James, P.</b> [US/US]; 34 Devonshire Drive, Waterford, CT 06385 (US).</p> <p>(74) Agents: <b>SPIEGEL, Allen, J. et al.</b>; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p>		<p>(81) Designated States: <b>CA, FI, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</b></p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: <b>ARYLSULFONYL HYDROXAMIC ACID DERIVATIVES AS MMP AND TNF INHIBITORS</b></p> <p>(57) Abstract</p> <p>A compound of formula (I) wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and Ar are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases involving the production of TNF.</p> <p style="text-align: right;">(I)</p>			

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## ARYLSULFONYL HYDROXAMIC ACID DERIVATIVES AS MMP AND TNF INHIBITORS

### Background of the Invention

The present invention relates to arylsulfonyl hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor 10 (hereinafter also referred to as TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases involving the production of TNF.

15 This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefor.

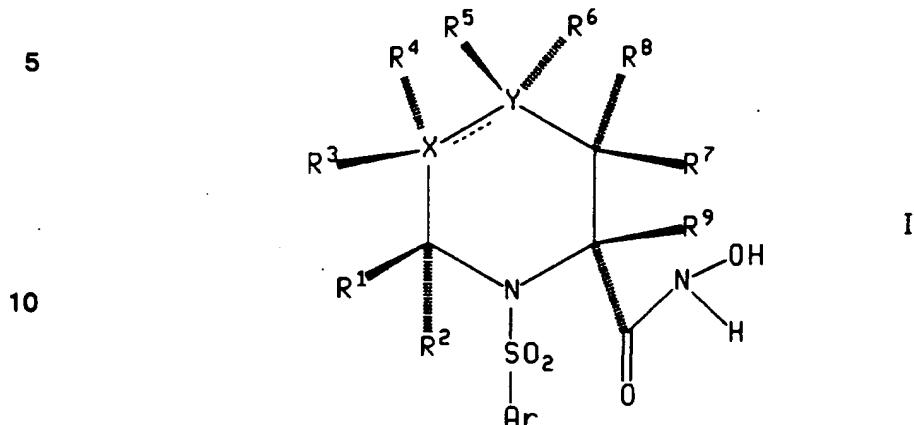
There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading 20 metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, 25 periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and 30 septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

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Summary of the Invention

The present invention relates to a compound of the formula



15 or the pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

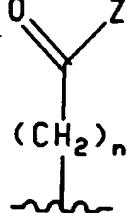
X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, sulfoxide, sulfone or nitrogen;

10 R<sup>1</sup>, R<sup>2</sup> R<sup>3</sup>, R<sup>4</sup> R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, trifluoromethyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>6</sub>-C<sub>10</sub>)arylothio, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, (C<sub>5</sub>-C<sub>9</sub>)heteroarylamino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylothio, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(hydroxymethylene), piperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)acylthio, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino or ((C<sub>1</sub>-C<sub>6</sub>)alkylamino)<sub>2</sub>; (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl (difluoromethylene), (C<sub>1</sub>-C<sub>3</sub>)alkyl(difluoromethylene)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>6</sub>-C<sub>10</sub>)arylthio, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, (C<sub>5</sub>-C<sub>9</sub>)heteroarylamino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylthio, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(hydroxymethylene), piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)

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5  $C_6$ )acylthio,  $(C_1-C_6)$ acyloxy,  $R^{13}(C_1-C_6)$ alkyl wherein  $R^{13}$  is  $(C_1-C_6)$ acylpiperazino,  $(C_6-C_{10})$ arylpiperazino,  $(C_5-C_9)$ heteroaryl(piperazino,  $(C_1-C_6)$ alkylpiperazino,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkylpiperazino,  $(C_5-C_9)$ heteroaryl( $C_1-C_6$ )alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl,  $(C_1-C_6)$ alkylpiperidyl,  $(C_6-C_{10})$ aryl(piperidyl,  $(C_6-C_9)$ heteroaryl(piperidyl,  $(C_1-C_6)$ alkylpiperidyl( $C_1-C_6$ )alkyl,  $(C_6-C_9)$ heteroaryl(piperidyl( $C_1-C_6$ )alkyl or  $(C_1-C_6)$ acylpiperidyl;



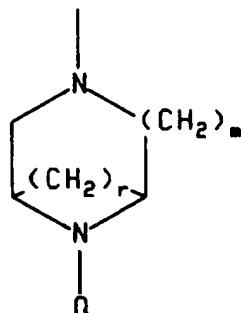
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wherein n is 0 to 6;

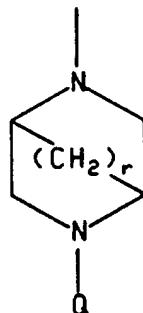
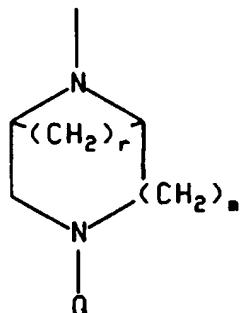
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$C_6$ )alkyl,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkyl and  $(C_5-C_9)$ heteroaryl( $C_1-C_6$ )alkyl; and  $R^{19}$  is  $R^{22}O$  or  $R^{22}R^{23}N$  wherein  $R^{22}$  and  $R^{23}$  are each independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkyl and  $(C_5-C_9)$ heteroaryl( $C_1-C_6$ )alkyl; or  $R^{14}$  and  $R^{15}$ , or  $R^{20}$  and  $R^{21}$ , or  $R^{22}$  and  $R^{23}$  may be taken together to form an 5 azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl,  $(C_1-C_6)$ acylpiperazinyl,  $(C_1-C_6)$ alkylpiperazinyl,  $(C_6-C_{10})$ arylpiperazinyl,  $(C_5-C_9)$ heteroaryl(piperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of

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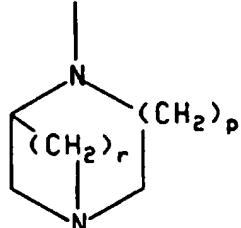


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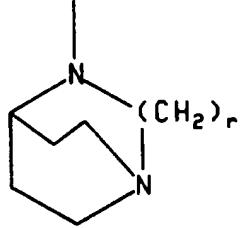
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d

e

wherein  $r$  is 1, 2 or 3;

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$m$  is 1 or 2;

$p$  is 0 or 1; and

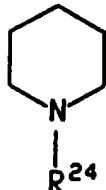
$Q$  is hydrogen,  $(C_1-C_3)$ alkyl,  $(C_1-C_6)$ acyl or  $(C_1-C_6)$ alkoxy carbamoyl;

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or R<sup>1</sup> and R<sup>2</sup>, or R<sup>3</sup> and R<sup>4</sup>, or R<sup>5</sup> and R<sup>6</sup> may be taken together to form a carbonyl;

or R<sup>1</sup> and R<sup>2</sup>, or R<sup>3</sup> and R<sup>4</sup>, or R<sup>5</sup> and R<sup>6</sup>, or R<sup>7</sup> and R<sup>8</sup> may be taken together to form a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or

5 a group of the formula



10

wherein R<sup>24</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)acyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl; and

Ar is (C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, each of which may be optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkyl, one or two (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy or (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy;

with the proviso that R<sup>7</sup> is other than hydrogen only when R<sup>8</sup> is other than hydrogen;

with the proviso that R<sup>6</sup> is other than hydrogen only when R<sup>5</sup> is other than hydrogen;

20 with the proviso that R<sup>3</sup> is other than hydrogen only when R<sup>4</sup> is other than hydrogen;

with the proviso that R<sup>2</sup> is other than hydrogen only when R<sup>1</sup> is other than hydrogen;

25 with the proviso that when R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 2- or 6- positions;

with the proviso that when X is nitrogen, R<sup>4</sup> is not present;

with the proviso that when X is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R<sup>1</sup>, R<sup>2</sup>, R<sup>5</sup> and R<sup>6</sup>, is a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 4- or 6- positions;

30 with the proviso that when Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R<sup>3</sup>, R<sup>4</sup>, R<sup>7</sup> and R<sup>8</sup>, are independently a

substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 3- or 5- positions;

with the proviso that when X is oxygen, sulfur, sulfoxide or sulfone, R<sup>3</sup> and R<sup>4</sup> are not present;

5 with the proviso that when Y is nitrogen, R<sup>4</sup> is not present;

with the proviso that when Y is oxygen, sulfur, sulfoxide or sulfone, R<sup>5</sup> and R<sup>6</sup> are not present;

with the proviso that when Y is nitrogen, R<sup>6</sup> is not present;

10 with the proviso that when the broken line represents a double bond, R<sup>4</sup> and R<sup>6</sup> are not present;

with the proviso that when R<sup>3</sup> and R<sup>5</sup> are independently a substituent comprising a heteroatom when the broken line represents a double bond, the heteroatom cannot be directly bonded to positions X and Y;

15 with the proviso that when either the X or Y position is oxygen, sulfur, sulfoxide, sulfone or nitrogen, the other of X or Y is carbon;

with the proviso that when X or Y is defined by a heteroatom, the broken line does not represent a double bond;

20 with the proviso that when R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are all defined by hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, either X or Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen, or the broken line represents a double bond.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

25 The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluoro, chloro, cyano, nitro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, 30 (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy and (C<sub>1</sub>-C<sub>6</sub>)alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyrrol, thienyl, isothiazolyl, imidazolyl, benzimidazolyl,

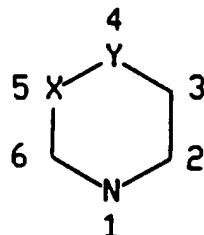
tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents independently selected from the group consisting of fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy and (C<sub>1</sub>-C<sub>6</sub>)alkyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The positions on the ring of formula I, as used herein, are defined as follows:

15



The preferred conformation of the compound of formula I includes hydroxamic acid axially disposed in the 2-position.

20 The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein Y is oxygen, nitrogen or sulfur.

25 Other preferred compounds of formula I include those wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

Other preferred compounds of formula I include those wherein R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

30 Other preferred compounds of formula I include those wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are hydrogen.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

More preferred compounds of formula I include those wherein Y is oxygen, Ar 5 is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

10 More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>5</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

15 More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>5</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

More preferred compounds of formula I include those wherein Y is carbon, Ar 20 is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>5</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>5</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

25 More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>5</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkylamino.

More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkylamino.

Specific preferred compounds of formula I include the following:

30 (2R,3S)-N-hydroxy-3-ethynyl-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(5-methoxythiophene-2-yl-ethynyl)-piperidine-2-carboxamide;

(2R,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(3-pyridin-3-yl-prop-2-ynyl)-piperidine-2-carboxamide;

(2S,3R)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-2-pyridine-3-yl-morpholine-3-carboxamide;

5 (2S,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-morpholine-3-carboxamide;

(2R,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(4-phenylpyridine-2-yl)-10 piperidine-2-carboxamide;

(2S,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-(4-phenylpyridine-2-yl)-morpholine-2-carboxamide;

(2R,3S)-N-hydroxy-3-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide; and

15 (2S,3R)-N-hydroxy-2-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-3-carboxamide.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other 20 diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and 25 a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

30 The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the

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**production of tumor necrosis factor (TNF) in a mammal, including a human, comprising  
administering to said mammal an amount of a compound of claim 1 or a  
pharmaceutically acceptable salt thereof, effective in treating such a condition.**

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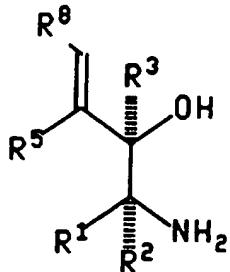
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $n$  and  $Ar$  in the reaction Schemes and the discussion that follow are defined as above.

5

Preparation 1

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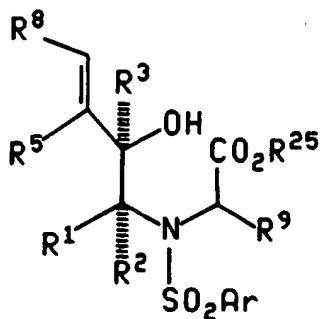


XVI

15

↓ 1

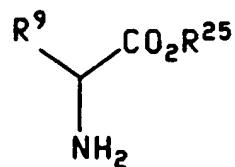
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VI

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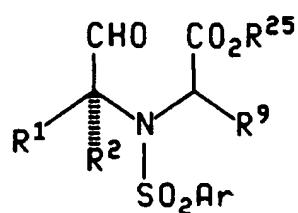
Preparation 2

XVIII

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1

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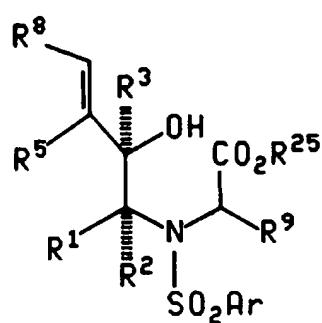


XVII

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2

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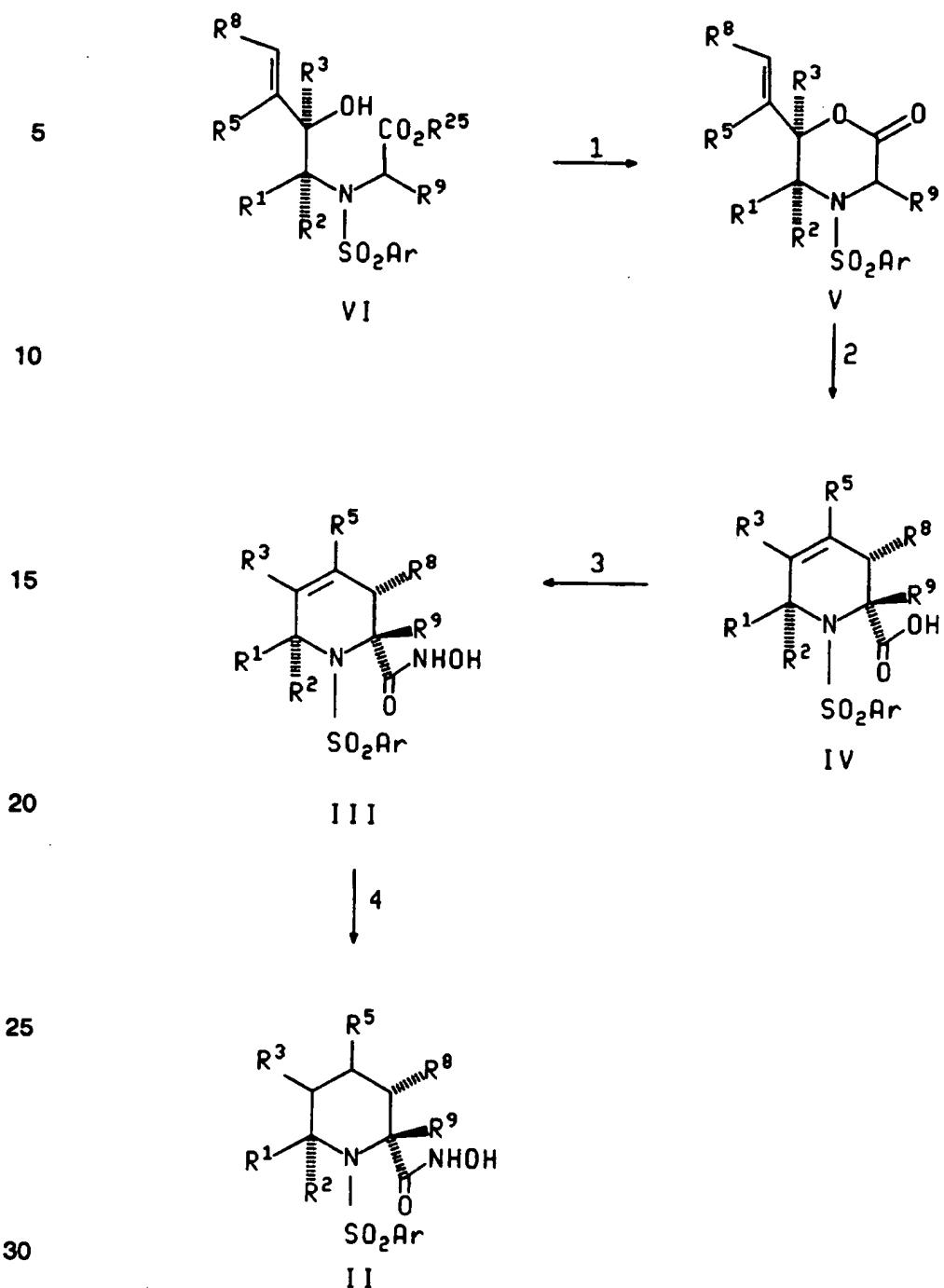


VI

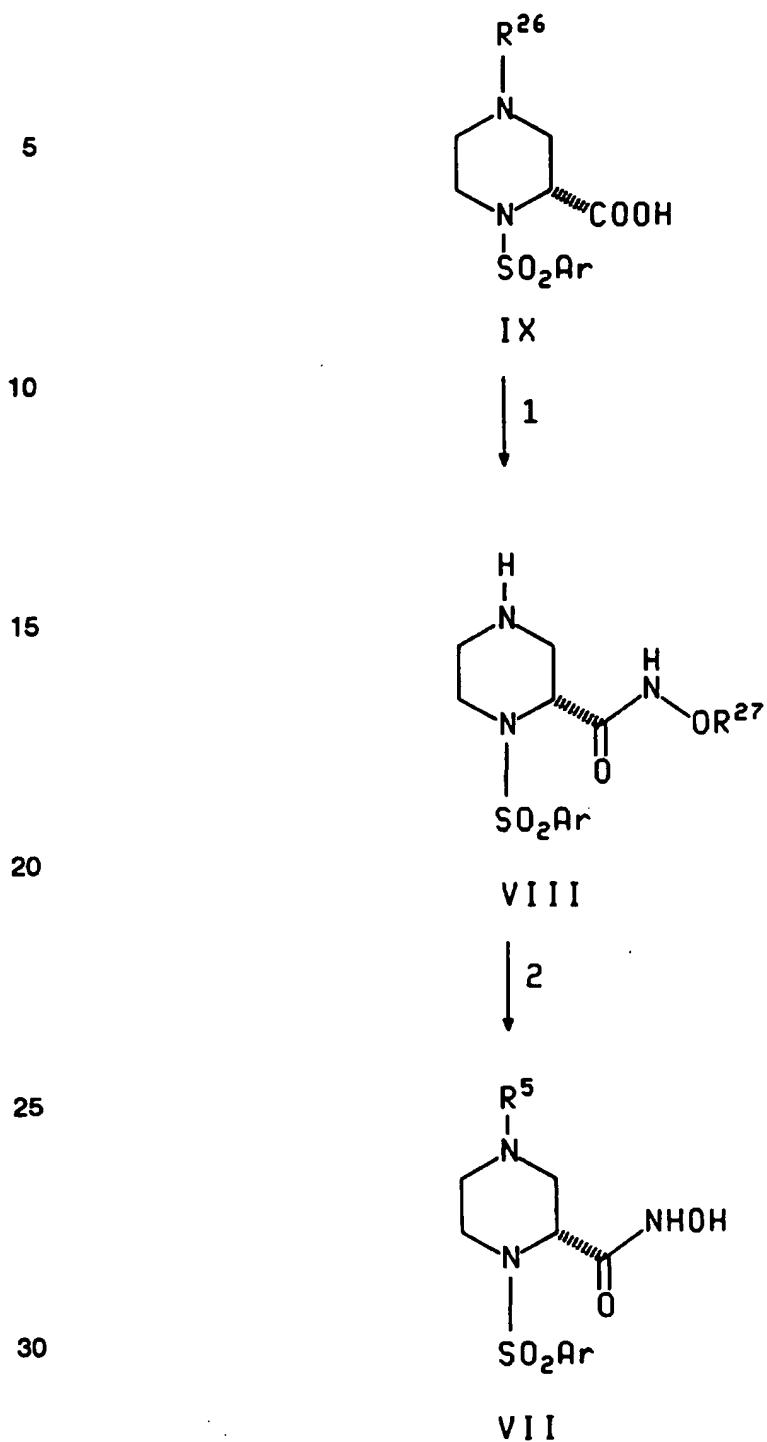
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-13-

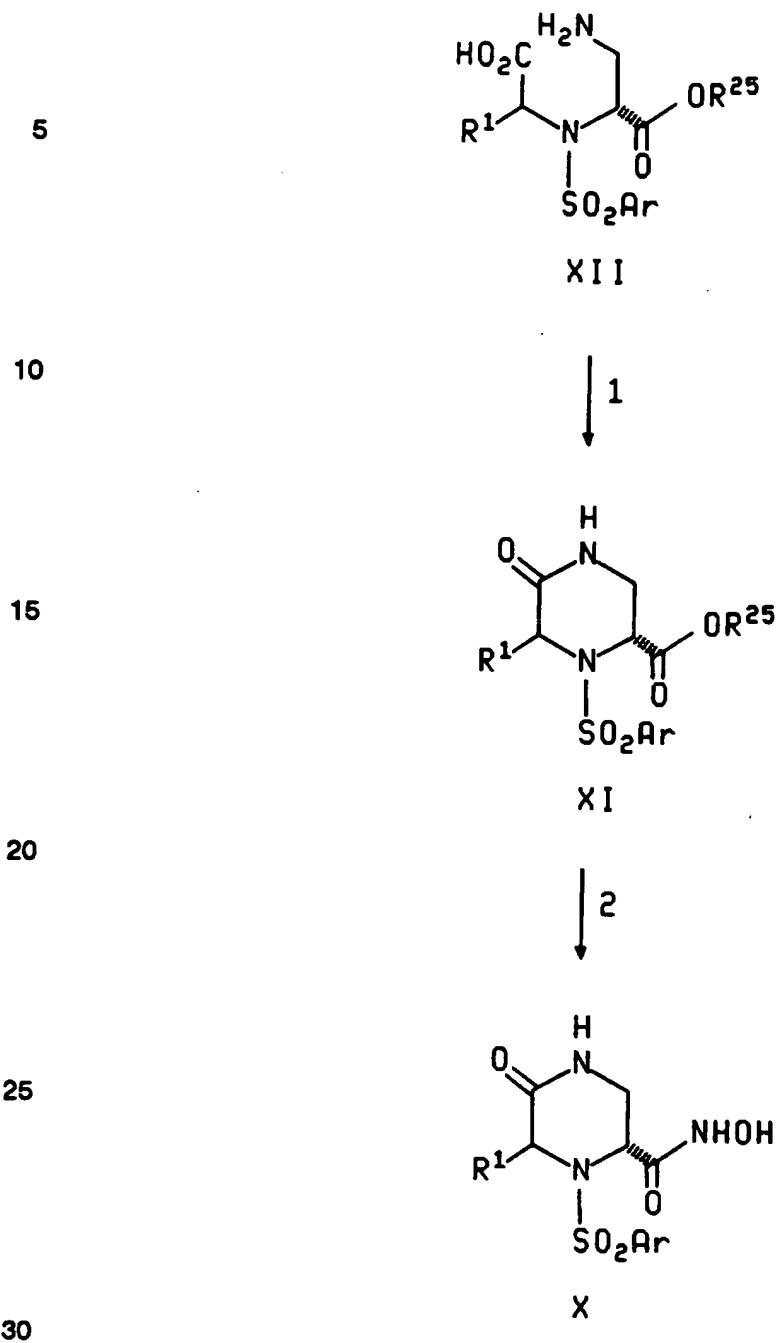
### **Scheme 1**



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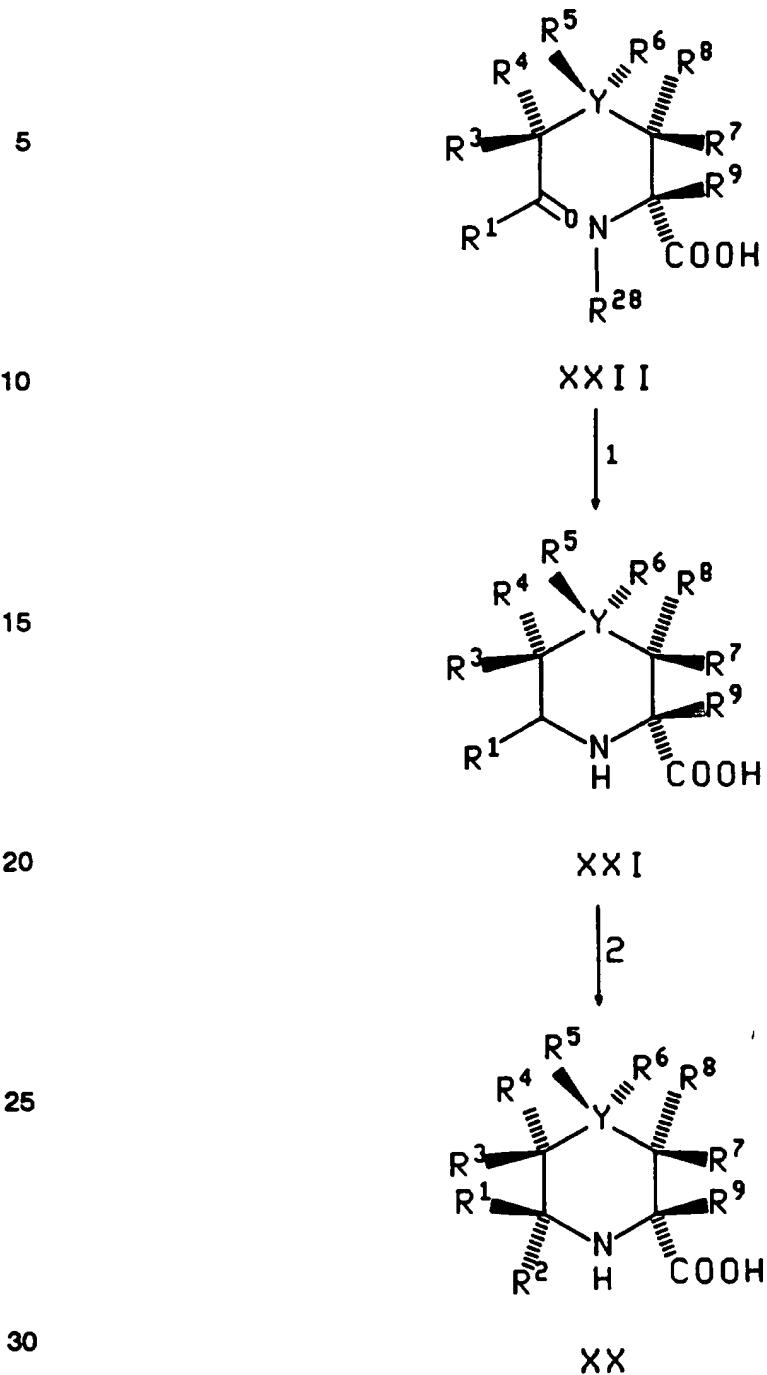
Scheme 2

-15-

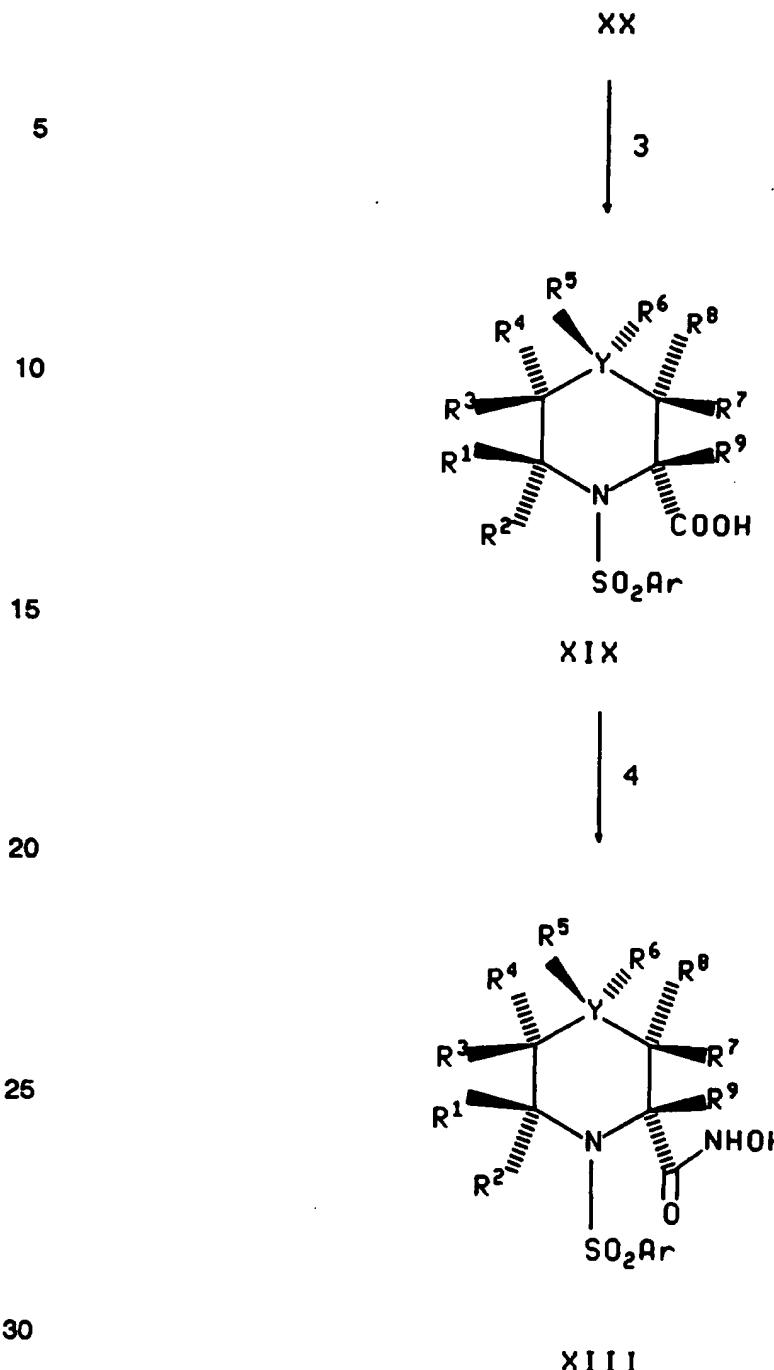
Scheme 3

-16-

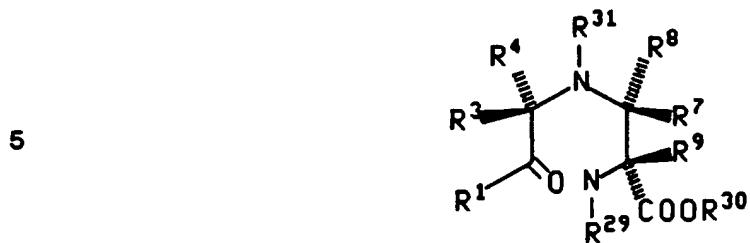
#### **Scheme 4**



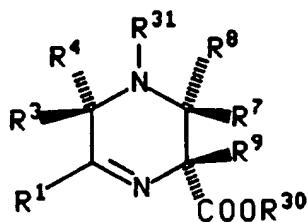
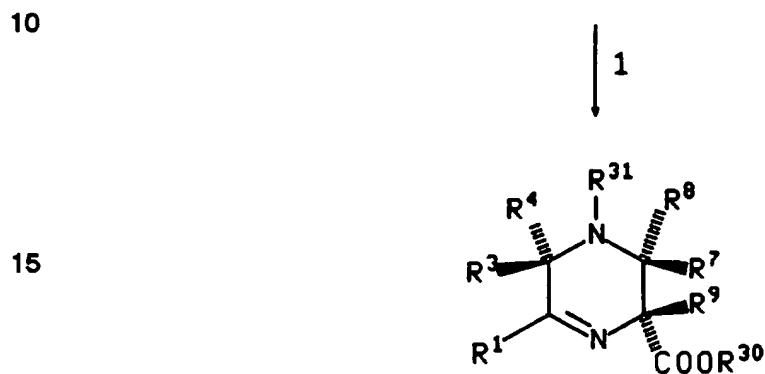
-17-

Scheme 4 continued

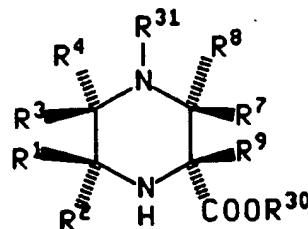
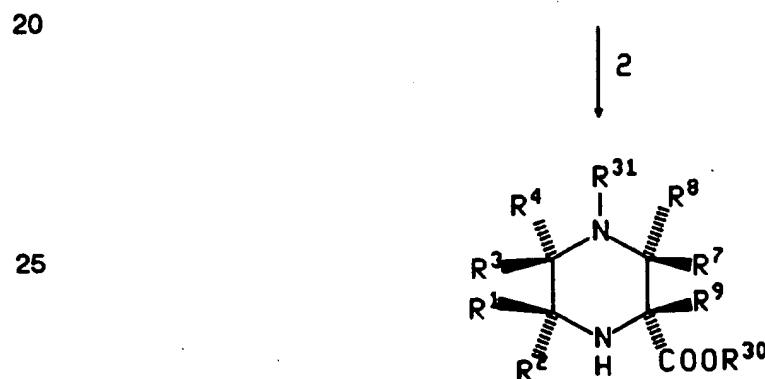
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Scheme 5

XXVI



XXV



30

XXIV

-19-

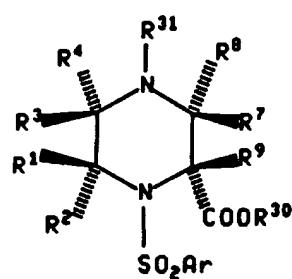
Scheme 5 continued

XXIV

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3

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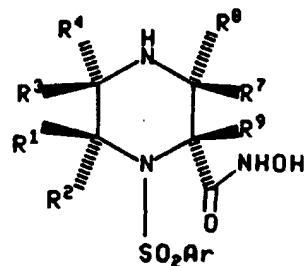


XXIII

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4

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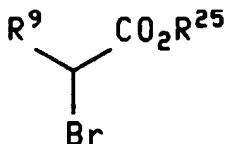


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XIV

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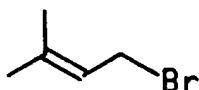
In reaction 1 of Preparation 1, the compound of formula XVI is converted to the corresponding hydroxy ester compound of formula VI by first reacting XVI with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature. The compound so formed is further reacted with a compound of the formula



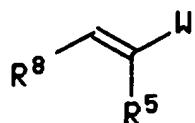
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wherein  $\text{R}^{25}$  is carbobenzyloxy,  $(\text{C}_1\text{-C}_6)$ alkyl, benzyl, allyl or tert-butyl, in the presence of sodium hexamethyldisilazane and a tetrahydrofuran-dimethylformamide solvent mixture at a temperature between about -20°C to about 20°C, preferably about 0°C, to form the hydroxy ester compound of formula VI.

15 In reaction 1 of Preparation 2, the amine compound of formula XVIII, wherein  $\text{R}^{25}$  is as defined above, is converted to the corresponding arylsulfonyl amine compound of formula XVII by (1) reacting XVIII with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran, or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature, (2) reacting the compound so formed with a compound of the formula



25 in the presence of sodium hexamethyldisilazane and a tetrahydrofuran-dimethylformamide solvent mixture at a temperature between about -20°C to about 20°C, preferably about 0°C, and (3) further reacting the compound so formed with ozone in a methylene chloride-methanol solution at a temperature between about -90°C to about -70°C, preferably about -78°C. The unstable ozonide compound so formed 30 is then reacted with triphenylphosphine to form the arylsulfonyl amine compound formula XVII. In Reaction 2 of Preparation 2, the arylsulfonyl amine compound of formula XVII is converted to the corresponding hydroxy ester compound of formula VI by reacting XVII with a compound of the formula



5 wherein W is lithium, magnesium, copper or chromium.

In reaction 1 of Scheme 1, the compound of formula VI, wherein the R<sup>25</sup> protecting group is carbobenzyloxy, (C<sub>6</sub>-C<sub>6</sub>) alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding morpholinone compound of formula V by lactonization and subsequent Claisen rearrangement of the compound of formula VI. The reaction is 10 facilitated by the removal of the R<sup>25</sup> protecting group from the compound of formula VI is carried out under conditions appropriate for that particular R<sup>25</sup> protecting group in use. Such conditions include: (a) treatment with hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R<sup>25</sup> is carbobenzyloxy, (b) saponification where R<sup>25</sup> is lower alkyl, (c) hydrogenolysis where R<sup>25</sup> is benzyl, (d) 15 treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid, where R<sup>25</sup> is tert-butyl, or (e) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R<sup>25</sup> is allyl.

In reaction 2 of Scheme 1, the morpholinone compound of formula V is converted to the carboxylic acid compound of formula IV by reacting V with lithium 20 hexamethyldisilazane in an aprotic solvent, such as tetrahydrofuran, at a temperature between about -90°C to about -70°C, preferably about -78°C. Trimethylsilyl chloride is then added to the reaction mixture and the solvent, tetrahydrofuran, is removed in vacuo and replaced with toluene. The resulting reaction mixture is heated to a 25 temperature between about 100°C to about 120°C, preferably about 110°C, and treated with hydrochloric acid to form the carboxylic acid compound of formula IV.

In reaction 3 of Scheme 1, the carboxylic acid compound of formula IV is converted to the corresponding hydroxamic acid compound of formula III by treating IV with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as dimethylformamide, followed by the addition of hydroxylamine 30 to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated *in situ* from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively, a protected derivative of hydroxylamine or its salt

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form, where the hydroxyl group is protected as a tert-butyl, benzyl or allyl ether, may be used in the presence of (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate and a base, such as N-methylmorpholine. Removal of the hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. N,O-bis(4-methoxybenzyl)hydroxylamine may also be used as the protected hydroxylamine derivative where deprotection is achieved using a mixture 5 of methanesulfonic acid and trifluoroacetic acid.

10

In reaction 4 of Scheme 1, the hydroxamic acid compound of formula III is converted, if desired, to the corresponding piperidine compound of formula II by treating III with hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon.

15 In reaction 1 of Scheme 2, the arylsulfonylpiperazine compound of formula IX, wherein R<sup>26</sup> is carbobenzyloxy, benzyl or carbotertbutyloxy, is converted to the compound of formula VIII by reacting IX with a protected derivative of hydroxylamine of the formula.



20 wherein R<sup>27</sup> is tertbutyl, benzyl or allyl, in the presence of dicyclohexylcarbodiimide, dimethylaminopyridine and an aprotic solvent, such as methylene chloride. The R<sup>26</sup> protecting group is chosen such that it may be selectively removed in the presence of an without loss of the R<sup>27</sup> protecting group, therefore, R<sup>26</sup> cannot be the same as R<sup>27</sup>. Removal of the R<sup>26</sup> protecting group from the compound of formula IX is carried out 25 under conditions appropriate for that particular R<sup>26</sup> protecting group in use. Such conditions include: (a) treatment with a hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R<sup>26</sup> is carbobenzyloxy, (b) hydrogenolysis where R<sup>26</sup> is benzyl or (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid where R<sup>26</sup> is carbotertbutyloxy.

30 In reaction 2 of Scheme 2, the compound of formula VIII is converted to the corresponding hydroxamic acid compound of formula VII, wherein R<sup>5</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, by reacting, if desired, VIII with an alkylhalide when R<sup>5</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl. Subsequent removal of the R<sup>27</sup> hydroxylamine protecting group is carried out by

hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride.

5 In reaction 1 of Scheme 3, the arylsulfonylamine compound of formula XII, wherein R<sup>26</sup> is as defined above, is converted to the corresponding piperazine compound of formula XI by reacting XII with a carbodiimide and a base, such as triethylamine. The compound of formula XI is further reacted to give the hydroxamic acid compound of formula X according to the procedure described above in reaction 10 3 of Scheme 1.

In reaction 1 of Scheme 4, removal of the R<sup>28</sup> protecting group and subsequent reductive amination of the compound of formula XXII, wherein Y is oxygen, sulfur or carbon, to give the corresponding imine compound of formula XXI is carried out under conditions appropriate for that particular R<sup>28</sup> protecting group in use. Such conditions 15 include those used above for removal of the R<sup>28</sup> protecting group in reaction 1 of Scheme 2.

In reaction 2 of Scheme 4, the imine compound of formula XXI is converted to the corresponding piperidine compound of formula XX by reacting XXI with a nucleophile of the formula R<sup>2</sup>M wherein M is lithium, magnesium halide or cerium 20 halide. The reaction is carried out in ether solvents, such as diethyl ether or tetrahydrofuran, at a temperature between about -78°C to about 0°C, preferably about -70°C.

In reaction 3 of Scheme 4, the sulfonation of the piperidine compound of formula XX to give the corresponding arylsulfonylpiperidine compound of formula XIX 25 is carried out by reacting XX with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature.

In reaction 4 of Scheme 4, the arylsulfonylpiperidine compound of formula XIX is converted to the hydroxamic acid compound of formula XIX according to the 30 procedure described above in reaction 3 of Scheme 1.

In reaction 1 of Scheme 5, the compound of formula XXVI, wherein the R<sup>29</sup> and R<sup>31</sup> protecting groups are each independently selected from the group consisting of carbobenzyloxy, benzyl and carbotertbutyloxy and R<sup>30</sup> is carbobenzyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl,

benzyl, allyl or tert-butyl, is converted to the corresponding imine compound of formula **XXV** by the removal of the  $R^{29}$  protecting group and subsequent reductive amination of the compound of formula **XXVI**. The  $R^{29}$  protecting group is chosen such that it may be selectively removed in the presence of and without loss of the  $R^{31}$  protecting group.

- 5 Removal of the  $R^{29}$  protecting group from the compound of formula **XXVI** is carried out under conditions appropriate for that particular  $R^{29}$  protecting group in use which will not affect the  $R^{31}$  protecting group. Such conditions include; (a) treatment with hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where  $R^{29}$  is carbobenzyloxy and  $R^{31}$  is tert-butyl, (b) saponification where  $R^{29}$  is  $(C_1\text{-}C_6)$ alkyl and  $R^{31}$  is tert-butyl, (c) hydrogenolysis where  $R^{29}$  is benzyl and  $R^{31}$  is  $(C_1\text{-}C_6)$ alkyl or tert-butyl, (d) treatment with a strong acid such as trifluoroacetic acid or hydrochloric acid where  $R^{29}$  is tert-butyl and  $R^{31}$  is  $(C_1\text{-}C_6)$ alkyl, benzyl or allyl, or (e) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where  $R^{29}$  is allyl and  $R^{31}$  is  $(C_1\text{-}C_6)$ alkyl, benzyl or tert-butyl. The  $R^{30}$  protective group may be selected such that it is removed in the same reaction step as the  $R^{29}$  protecting group.

In reaction 2 of Scheme 5, the imine compound of formula **XXV** is converted to the corresponding compound of formula **XXIV** by reacting **XXV** with a nucleophile of the formula  $R^2M$  wherein M is lithium, magnesium halide or calcium halide. The 20 reaction is carried out in ether solvents, such as diethyl ether or tetrahydrofuran, at a temperature between about  $-78^\circ\text{C}$  to about  $0^\circ\text{C}$ , preferably about  $-70^\circ\text{C}$ .

In reaction 3 of Scheme 5, the sulfonation of the piperidine compound of formula **XXIV** to give the corresponding arylsulfonylpiperidine compound of formula **III** is carried out according to the procedure described above in reaction 3 of Scheme 4.

- 25 In reaction 4 of Scheme 5, the arylsulfonylpiperidine compound of formula **XXIII** is converted to the hydroxamic acid compound of formula **XIV** by (1) removing the  $R^{30}$ , if needed, and  $R^{31}$  protecting groups from **XXIII** followed by (2) reacting **XXIII** according to the procedure described above in reaction 3 of Scheme 1. Removal of the  $R^{30}$  and  $R^{31}$  protecting groups from the compound of formula **XXIII** is carried out under 30 conditions appropriate for that particular  $R^{30}$  and  $R^{31}$  protecting group in use. Such conditions include those used above for removal of the  $R^{26}$  protecting group in reaction 1 of Scheme 1.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

5

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

10

15 Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10  $\mu$ g trypsin per 100  $\mu$ g of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50  $\mu$ g/10  $\mu$ g trypsin) of soybean trypsin inhibitor is added.

20

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM  $\longrightarrow$  120  $\mu$ M  $\longrightarrow$  12  $\mu$ M  $\longrightarrow$  1.2  $\mu$ M  $\longrightarrow$  0.12  $\mu$ M

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

25

Collagenase is diluted to 400 ng/ml and 25  $\mu$ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

30

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub>) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20  $\mu$ M in assay buffer. The assay is

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initiated by the addition of 50  $\mu$ l substrate per well of the microfluor plate to give a final concentration of 10  $\mu$ M.

Fluorescence readings (360 nm excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with 5 a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC<sub>50</sub> values. The zero time is used as a 10 blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone  $\times$  100). IC<sub>50</sub>'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

15 If IC<sub>50</sub>'s are reported to be <0.03  $\mu$ M then the inhibitors are assayed at concentrations of 0.3  $\mu$ M, 0.03  $\mu$ M, 0.03  $\mu$ M and 0.003  $\mu$ M.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub> substrate (10  $\mu$ M) under the same conditions as inhibition of 20 human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30  $\mu$ M, 3  $\mu$ M, 0.3  $\mu$ M and 0.03  $\mu$ M. Each 25 concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC<sub>50</sub>'s are determined as per inhibition of human collagenase (MMP-1). If IC<sub>50</sub>'s are reported to be less than 0.03  $\mu$ M, then the inhibitors are assayed at final 30 concentrations of 0.3  $\mu$ M, 0.03  $\mu$ M, 0.003  $\mu$ M and 0.003  $\mu$ M.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, *Anal. Biochem.* **147**, 437-440 5 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-SCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>]CO-Leu-Gly-OC<sub>2</sub>H<sub>5</sub>] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1  $\mu$ l of a 10 mg/ml trypsin stock per 26  $\mu$ g of stromelysin. The trypsin and stromelysin are 10 incubated at 37°C for 15 minutes followed by 10  $\mu$ l of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250  $\mu$ l of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25  $\mu$ g/ml. Ellman's reagent 15 (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50  $\mu$ l per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50  $\mu$ L to the appropriate wells yields final concentrations of 3  $\mu$ M, 0.3  $\mu$ M, 0.003  $\mu$ M, and 0.0003  $\mu$ M. All conditions are 20 completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50  $\mu$ l to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm 25 with a Molecular Devices UVmax plate reader.

IC<sub>50</sub> values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 30 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20 $\mu$ M zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

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10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30  $\mu$ M, 3  $\mu$ M, 5 0.3  $\mu$ M, and 0.03  $\mu$ M.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub>) is prepared as for inhibition of human collagenase (MMP-1) and 50  $\mu$ l is added to each well to give a final assay concentration of 10  $\mu$ M. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

10 Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC<sub>50</sub>'s are determined as per inhibition of human collagenase (MMP-1). If IC<sub>50</sub>'s are reported to be less than 0.03  $\mu$ M, inhibitors are then assayed at final concentrations of 0.3  $\mu$ M, 0.03  $\mu$ M, 0.003  $\mu$ M and 0.0003  $\mu$ M.

15 Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following *in vitro* assay:

20 Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10<sup>6</sup> /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes 25 ranged from 17 to 24% of the total cells in these preparations.

180 $\mu$ l of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200 $\mu$ l. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO<sub>2</sub> incubator, plates were removed and 30 centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF $\alpha$  using the R&D ELISA Kit.

For administration to humans for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be

used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition 5 of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 10 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, 15 together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight 20 polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

25 For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if 30 necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these

solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is possible to administer the compounds of the present invention topically, e.g., when treating inflammatory conditions of the skin and this may be done 5 by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

#### EXAMPLE 1

10        (+)-(2R\*,3R\*)-(N-hydroxy)-1-(4-methoxy-benzenesulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxamide.

(a) To a solution of (E)-1-amino-3-pentent-2-ol (2.0 grams, 10.0 mmol) in 15 methylene chloride (50 ml) is added triethylamine (160  $\mu$ L, 11.0 mmol) followed by 4-methoxybenzenesulfonyl chloride (2.07 grams, 10.0 mmol). The mixture is stirred at room temperature for 12 hours and diluted with ethyl acetate. The mixture is washed 20 with water, 10% citric acid, dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes) to provide (N-(2-hydroxy-pent-3-enyl)-4-methoxybenzenesulfonamide.

(b) To a solution of (+)-(E)-N-(2-hydroxy-pent-3-enyl)-4-20 methoxybenzenesulfonamide (1.2 grams, 4.42 mmol) in tetrahydrofuran-dimethylformamide (10 mL, ca. 3:1) at 0°C is added sodium bis(trimethylsilyl)amide (4.9 mL, 1.0 M solution in tetrahydrofuran). After 10 minutes, t-butylbromoacetate (786 mL, 4.83 mmol) is added. The mixture is warmed to room temperature, stirred for 1 hour and quenched with saturated ammonium chloride solution. The mixture is extracted 25 with ethyl acetate and the combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 1:1 ethyl acetate-hexanes) to provide [(2-hydroxy-pent-3-enyl)-(4-methoxybenzenesulfonyl)-amino]-acetic acid t-butyl ester.

(c) To a solution of (+)-(E)-N-(2-hydroxy-pent-3-enyl)-4-30 methoxybenzenesulfonyl)-amino]-acetic acid t-butyl ester (900 mg, 2.43 mmol) in benzene (10 ml) is added trifluoroacetic acid (56  $\mu$ L, 0.73 mmol). The solution is heated at 80°C for 3 hours, cooled to room temperature and concentrated to provide

( $\pm$ )-(E)-4-(4-methoxybenzenesulfonyl)-6-propenylmorpholin-2-one which is used without further purification.

(d) To a solution of lithium bis(trimethylsilyl)amide (2.67 mmol, 1.0 M in tetrahydrofuran) in tetrahydrofuran (5.0 ml) at -78°C is added a solution of ( $\pm$ )-(E)-4-(4-methoxybenzenesulfonyl)-6-propenylmorpholine-2-one crude from the previous step.

5 After 15 minutes, trimethylsilyl chloride (1.53 ml, 12.15 mmol) is added and the mixture warmed to room temperature. The solvent is removed (in vacuo) and replaced with toluene (10 ml). The resulting mixture is heated at 110°C for 3 hours, cooled to room temperature and treated with 1N hydrochloric acid solution. After stirring for 10 minutes, the mixture is extracted with ethyl acetate and the combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide ( $\pm$ )-(2R\*, 3R\*)-1-(4-methoxybenzenesulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid.

10 (e) To a solution of ( $\pm$ )-(2R\*, 3R\*)-1-(4-methoxybenzenesulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid (100 mg, 0.36 mmol) in dimethylformamide (5 ml.) is added hydroxybentriazole (53 mg, 0.39 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (75 mg, 0.39 mmol). After 1 hour, hydroxylamine hydrochloride (75 mg, 1.08 mmol) is added followed by triethylamine (150  $\mu$ L, 1.08 mmol). After stirring overnight, the mixture is diluted with water and extracted with ethyl acetate. The combined extracts are dried, filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide ( $\pm$ )-(2R\*, 3R\*)-(N-hydroxy)-1-(4-methoxybenzenesulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxamide as a white solid.

15 Melting point 173°C (dec.). Mass spectrum (thermospray): m/Z 326 (m-C(O)N(H)OH, 100%, (m, 7%), (m+H, 30%), (m+NH<sub>4</sub>, 10%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, ppm):  $\delta$  7.72 (d, J = 8.9 Hz, 2H), 7.03 (d, J=8.9 Hz, 2H), 5.66 (dq, J=13.0, 2.7 Hz, 1H), 5.45 (dd, 13.0, 1.9 Hz), 4.37 (d, 7.0 Hz, 1H), 4.06-3.82 (m, 2H), 3.82 (s, 3H), 3.43-3.30 (m, 1H), 2.62-2.31 (m, 1H), 0.97 (d, 7.5 Hz, 3H).

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EXAMPLE 2N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide

(a) To a solution of glycine t-butyl ester (5.0 grams, 29.82 mmol) in 5 methylene chloride (50 ml) is added triethylamine (6.65 ml, 62.63 mmol) followed by 4-methoxybenzenesulfonyl chloride (29.82 mmol, 6.2 grams). The solution is stirred for 24 hours, diluted with water and extracted with ethyl acetate. The combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 6:1 hexane-ethyl acetate) to provide (4-methoxybenzenesulfonylamino) acetic acid t-butyl ester.

(b) To a solution of (4-methoxybenzenesulfonylamino) acetic acid t-butyl ester (3.0 grams, 10 mmol) in tetrahydrofuran-dimethylformamide (mL, ca. 3:1) at 0°C is added sodium bis(trimethylsilyl)amide (10.0 mL, 1.0 M solution in tetrahydrofuran). After 10 minutes, 4-bromo-2-methyl-2-butene (1.27  $\mu$ L, 11.0 mmol) is added. The 15 mixture is warmed to room temperature, stirred for 1 hour and quenched with saturated ammonium chloride solution. The mixture is extracted with ethyl acetate and the combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 1:1 ethyl acetate-hexanes) to provide [(4-methoxybenzenesulfonyl)-(3-methyl-but-2-enyl)-amino]-acetic acid t-butyl ester.

(c) Ozone is passed through a solution of [(4-methoxybenzenesulfonyl)-(3-methyl-but-2-enyl)-amino]-acetic acid t-butyl ester (2.0 grams, 5.4 mmol) in methylene chloride-methanol (50 mL, ca. 1:1) at -78°C until a blue color persisted. Triphenylphosphine (4.24 grams, 16.2 mmol) is added and the resulting solution is 25 stirred at room temperature for 3 hours. Concentration provided the crude product which is purified by silica gel chromatography (elution with 1:1 ethyl acetate-hexanes) to provide [(4-methoxybenzenesulfonyl)-(2-oxo-ethyl)-amino]-acetic acid t-butyl ester.

(d) To a slurry of chromium (II) chloride (1.3 grams, 10.49 mmol) in 30 dimethylformamide (20 ml) is added a suspension of nickel (II) chloride (0.026 mmol, 1 mg) in dimethylformamide (1 ml) followed by a mixture of (trans)- $\beta$ -iodostyrene (1.20 grams, 5.24 mmol) and [(4-methoxybenzenesulfonyl)-2-oxo-ethyl)-amino]acetic acid t-butyl ester (900 mg, 2.62 mmol) in dimethylformamide (5 ml). The resulting solution is stirred for three hours, diluted with water and extracted with ethyl acetate. The

combined extracts are washed with brine, dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 3:2 hexane-ethyl acetate) to provide  $(\pm)$ -(E)-[(2-hydroxy-4-phenyl-but-3-enyl)-(4-methoxybenzenesulphonyl)-amino]-acetic acid t-butyl ester.

5 (e)  $(\pm)$ -(E)-[(2-hydroxy-4-phenyl-but-3-enyl)-(4-methoxybenzenesulphonyl)-amino]-acetic acid t-butyl ester is subjected to the conditions described in Example 1c.

The crude product is recrystallized from chloroform to provide  $(\pm)$ -(E)-4-(4-methoxybenzenesulfonyl)-6-styryl-morpholin-2-one.

10 (f)  $(\pm)$ -(E)-4-(4-methoxybenzenesulfonyl)-6-styryl-morpholin-2-one is subjected to the conditions described in Example 1d. The crude product is purified by silica gel chromatography (elution with 2:1 hexane-ethyl acetate with 1% acetic acid) to provide  $(\pm)$ -(2R\*-3R\*)-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid.

15 (g)  $(\pm)$ -(2R\*-3R\*)-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid is subject to the conditions described in Example 1e. The crude product is purified by silica gel chromatography (elution with 1:1 hexane-ethyl acetate with 1% acetic acid) to provide N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide as a white solid. Melting point 151-154°C (dec.). Mass spectrum [PBMS w/C.I. (NH<sub>3</sub>)]: m/Z 388 (m+NH<sub>4</sub>, 100%). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.75 (d, J = 8.5 Hz, 2H), 7.38-7.12 (m, 5H), 7.04 (d, J = 8.5 Hz, 2H), 5.91 (d, J = 8.9 Hz, 1H), 5.28 (d, J = 9.9 Hz, 1H), 4.89 (s, H<sub>2</sub>O), 4.57 (d, 6.8 Hz, 1H), 4.07 (ABq, J<sub>AB</sub> = 18.0 Hz, Δv AB = 39.1 Hz, 2H), 3.85 (o, 3H), 3.39 (bs, CD<sub>3</sub>OD).

### EXAMPLE 3

$(\pm)$ -(2R\*-3R\*)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-piperidine-2-carboxamide

25 (a) To a solution of  $(\pm)$ -(2R\*-3R\*)-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid (65 mg, 0.17 mmol) (from Example 20), is added benzylhydroxylamine hydrochloride (32 mg, 0.20 mmol), dicyclohexylcarbodiimide (41 mg, 0.20 mmol) and dimethylaminopyridine (27 mg, 0.22 mmol). The resulting mixture is stirred overnight, diluted with ethyl acetate and filtered through Celite™ and evaporated. The crude product is purified by chromatography elution with 1:1 hexane-ethyl acetate to provide  $(\pm)$ -(2R\*-3R\*)-N-benzyloxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide.

(b) To a solution of ( $\pm$ )-(2R\*-3R\*)-N-benzyloxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide (35 mg, 0.073 mmol) in ethanol (5 ml) is added 10% palladium on carbon (10 mg, 5 mol). The flask is evacuated and backfilled with hydrogen (repeated two times). The reaction 5 mixture is then stirred for 1 hour at which time it is filtered through Celite™ and concentrated. The product ( $\pm$ -2R\*-3R\*)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenylpiperidine-2-carboxamide was collected as a white solid. Melting point 163°C (dec). Mass spectrum [PBMS w/C.I. (NH<sub>3</sub>)]: m/Z 390 (m+H<sub>2</sub>), (m+NH<sub>4</sub>). <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.73 (d, J = 8.9 Hz, 2H), 7.31-7.37 (m, 5H), 7.04 (d, 8.9 Hz, 2H), 4.89 (s, 10 H<sub>2</sub>O), 4.34 (d, J = 5.4 Hz, 1H), 3.86 (s, 3H), 3.74-3.63 (m, 2H), 3.31 (bs, CD<sub>3</sub>OD), 2.99-2.90 (m, 1H), 2.58-2.52 (m, 1H), 1.94-1.88 (m, 1H), 1.67-1.60 (m, 2H).

#### EXAMPLE 4

##### (+)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide hydrochloride

15 (a) To a solution of ( $\pm$ )-4-benzyloxycarbonyl-2-piperazinecarboxylic acid (1.90 grams, 7.2 mmol) in dioxane-water (10 ml, ca. 1:1) is added 1N sodium hydroxide solution (15 ml, 15 mmol) followed by 4-methoxybenzenesulfonyl chloride. The solution is stirred for 1 hour, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The combined extracts are dried (sodium sulfate), filtered and concentrated. The crude 20 product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide ( $\pm$ )-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxylic acid.

25 (b) To a solution of ( $\pm$ )-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxylic acid (100 mg, 0.23 mmol) in methylene chloride (5 ml) is added O-t-butyloxylamine hydrochloride (35 mg, 0.28 mmol), dimethylaminopyridine (37 mg, 0.30 mmol), and dicyclohexycarbodiimide (57 mg, 0.28 mmol). After stirring overnight, the reaction is diluted with hexanes and the precipitated solid filtered off. The solution is concentrated and the crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide 30 ( $\pm$ )-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxamide.

(c) To a solution of ( $\pm$ )-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxamide (68 mg, 0.134 mmol), in methanol (6 ml)

is added 10% palladium on carbon (7 mg). The flask is evacuated and backfilled with hydrogen (repeated 2 times). The reaction mixture is then stirred for 1 hour at which time it is filtered through Celite™ and concentrated. The product (+)-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide is used without any further purification.

5 (d) To a solution of (+)-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide (30 mg, in dichloroethane is added ethanol (1 drop). The solution is cooled to -10°C and hydrogen chloride gas is bubbled through for 5 minutes. The reaction is then sealed and stirred for 24 hours at which time the volume 10 is reduced to 1/3 by evaporation and the precipitated solids are filtered and dried (in vacuo) to give (+)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide hydrochloride as a white solid. Melting point 167 °C. (dec.). Mass spectrum (thermospray): m/Z 343 (m + 1 100%). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 250 MHz, ppm): δ 7.76 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 3.87 (bs, H<sub>2</sub>O), 4.19 (d, J = 3.3 Hz, 1H), 3.87 15 (s, 3H), 3.58 (bd, J = 6.2 Hz, 1H), 3.42 (bd, J = 6.1 Hz, 1H), 3.30 (bs, CD<sub>3</sub>OD), 3.16 (d, J = 13.5 Hz, 1H), 2.87 (bd, J = 13.3 Hz, 1H), 2.69 (dd, J = 13.3, 3.0 Hz, 1H), 2.51 (dt, J = 12.5, 3.8 Hz, 1H).

#### EXAMPLE 5

##### N-hydroxy-1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide

20 (a) To a solution of (+)-benzyloxycarbonylamino-2-t-butoxycarbonyl aminopropionate (2.8 grams, 7.9 mmol) in methylene chloride (25 ml) at 0°C is added a solution of hydrochloric acid (g) dissolved in dioxane (25 ml). The solution is stirred at 0°C for 4 hours and then concentrated. The crude product 3-benzyloxycarbonylamino-2-amino-propionic acid methyl ester hydrochloride is used 25 without further purification.

(b) 3-benzyloxycarbonylamino-2-amino-propionic acid methyl ester hydrochloride is subjected to the conditions described in Example 1a. The crude product is purified by silica gel chromatography (elution with 1:1 hexane-ethyl acetate) to provide (+)-3-benzyloxycarbonylamino-2-(4-methoxybenzenesulfonylamino)-propionic acid methyl ester.

30 (c) (+)-3-benzyloxycarbonylamino-2-(4-methoxybenzene sulfonylamino)-propionic acid methyl ester is subjected to the conditions described in Example 1. The crude product is purified by silica gel chromatography (elution with 3:2 ethyl acetate-

hexane) to provide (±)-3-benzyloxycarbonylamino-2-[t-butoxycarbonylmethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester.

(d) (±)-3-benzyloxycarbonylamino-2-[t-butoxycarbonylmethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester is subjected to the 5 conditions described in Example 4c. The product 3-amino-2-[t-butoxycarbonylmethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester is used without further purification.

(e) To a solution of 3-amino-2-[t-butoxycarbonylmethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester (2.46 grams, 6.1 mmol) 10 in methylene chloride (20 ml) at 0°C is added trifluoroacetic acid (5 ml). The solution is stirred at 0°C for 12 hours and then concentrated. The crude product 3-amino-2-[carboxymethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester trifluoroacetic acid salt is used without further purification.

(f) To a solution of 3-amino-2-[carboxymethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester trifluoroacetic acid salt (2.11 grams, 6.1 mmol) in 15 methylene chloride (5 ml) is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.76 grams, 9.2 mmol) and triethylamine (3.4 ml, 24.4 mmol). The resulting mixture is stirred overnight, diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic layer is dried (sodium sulfate), filtered and concentrated. 20 The crude product is purified by silica gel chromatography (elution with ethyl acetate) to provide 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid methyl ester.

(g) To a solution of 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid methyl ester. (200 mg, 0.61 mmol) in methanol-tetrahydrofuran-water 25 (5 ml, ca. 6:2:1) at 0°C is added lithium hydroxide (64 mg, 1.53 mmol). The resulting mixture is stirred for 30 minutes, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid is used without further purification.

30 (h) To a solution of 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid (166 mg, 0.53 mmol) in methylene chloride (5 ml) is added 0-benzyloxylamine hydrochloride (255 mg, 1.6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.8 mmol) and triethylamine (370 µL 2.65

mmol). The resulting mixture is stirred overnight, diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic layer is dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 5% methanol in methylene chloride) to provide N-(benzyloxy)-1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide.

(i) N-(benzyloxy)-1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide is subjected to the conditions described in Example 4c to give N-hydroxy-1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide as a white solid. Mass spectrum (thermospray): m/Z 343 (m+H, 60%), (m+NH<sub>4</sub>, 17%). <sup>1</sup>H NMR (CD<sub>3</sub>OD), 250 MHz, ppm) δ7.79 (d, J = 8.9 Hz, 2H), 4.90 (s, H<sub>2</sub>O), 4.47 (dd, J = 5.0, 3.2 Hz, 1H), (4.03, s, 2H), 3.88 (s, 3H), 3.47 (dd, J = 13.4, 3.2 Hz, 1H), 3.35-3.30 (m, 1H), 3.30 (s, CD<sub>3</sub>OD)

#### EXAMPLE 6

##### N-hydroxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide

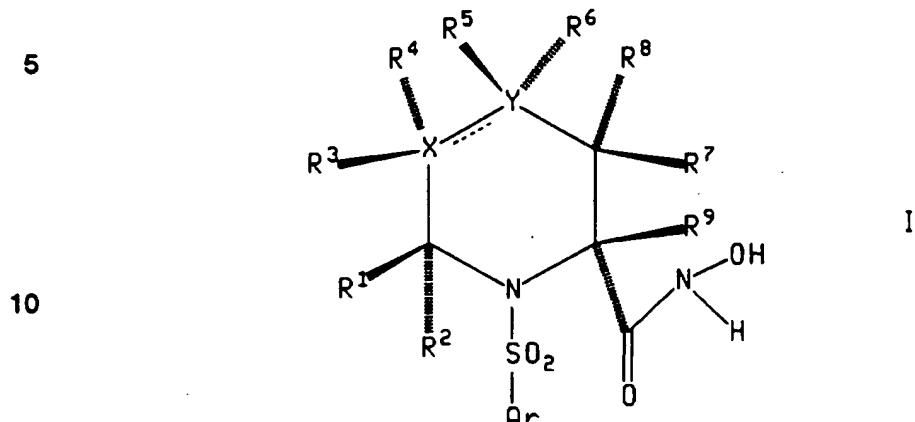
(a) morpholine-2-carboxylic acid is subjected to the conditions described in Example 4a to give 1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxylic acid.

(b) 1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxylic acid is subjected to the conditions described in example 5h to give N-benzyloxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide.

(c) N-benzyloxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide is subjected to the conditions described in Example 4c to give N-hydroxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide as a white foam. Mass spectrum (thermospray): m/Z 343 (m+H, 100%), [α]<sub>D</sub>: + 57° (c = 0.60, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>), 250 MHz, ppm) δ7.78 (bd, J = 8.0 Hz, 2H), 7.38 (bs, 1H), 7.01 (bd, J = 8.0 Hz, 2H), (4.34 (bs, J = 2H), 3.87 (s, 3H), 3.85-3.30 (m, 3H), 3.30-3.15 (m, 2H).

CLAIMS

## 1. A compound of the formula



15 or the pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

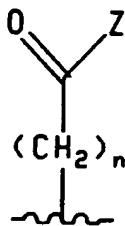
X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, sulfoxide, sulfone or nitrogen;

R<sup>1</sup>, R<sup>2</sup> R<sup>3</sup>, R<sup>4</sup> R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are selected from the group consisting of  
 20 hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, trifluoromethyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>6</sub>-C<sub>10</sub>)arylthio, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, (C<sub>5</sub>-C<sub>9</sub>)heteroarylamino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylthio, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(hydroxymethylene), piperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)acylthio, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino or ((C<sub>1</sub>-C<sub>6</sub>)alkylamino)<sub>2</sub>; (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl  
 30 (difluoromethylene), (C<sub>1</sub>-C<sub>3</sub>)alkyl(difluoromethylene)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>6</sub>-C<sub>10</sub>)arylthio, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, (C<sub>5</sub>-C<sub>9</sub>)heteroarylamino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylthio, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(hydroxymethylene), piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)

$C_6$ )acylthio,  $(C_1\text{--}C_6)$ acyloxy,  $R^{13}(C_1\text{--}C_6)$ alkyl wherein  $R^{13}$  is  $(C_1\text{--}C_6)$ acylpiperazino,  $(C_6\text{--}C_{10})$ arylpiperazino,  $(C_5\text{--}C_9)$ heteroarylpirazino,  $(C_1\text{--}C_6)$ alkylpirazino,  $(C_6\text{--}C_{10})$ aryl( $C_1\text{--}C_6$ )alkylpirazino,  $(C_6\text{--}C_9)$ heteroaryl( $C_1\text{--}C_6$ )alkylpirazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl,  $(C_1\text{--}C_6)$ alkylpiperidyl,  $(C_6\text{--}C_{10})$ arylpiridyl,  $(C_6\text{--}C_9)$ heteroarylpiridyl,  $(C_1\text{--}C_6)$ alkylpiridyl( $C_1\text{--}C_6$ )alkyl,  $(C_6\text{--}C_9)$ heteroarylpiridyl( $C_1\text{--}C_6$ )alkyl or  $(C_1\text{--}C_6)$ acylpiperidyl;

or a group of the formula



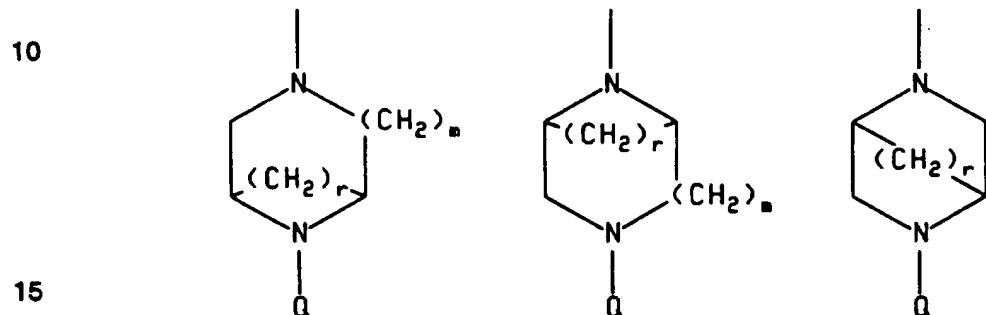
10

wherein n is 0 to 6;

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$C_6$ alkyl,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkyl and  $(C_5-C_9)$ heteroaryl( $C_1-C_6$ )alkyl; and  $R^{19}$  is  $R^{22}O$  or  $R^{22}R^{23}N$  wherein  $R^{22}$  and  $R^{23}$  are each independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkyl and  $(C_5-C_9)$ heteroaryl( $C_1-C_6$ )alkyl; or  $R^{14}$  and  $R^{15}$ , or  $R^{20}$  and  $R^{21}$ , or  $R^{22}$  and  $R^{23}$  may be taken together to form an

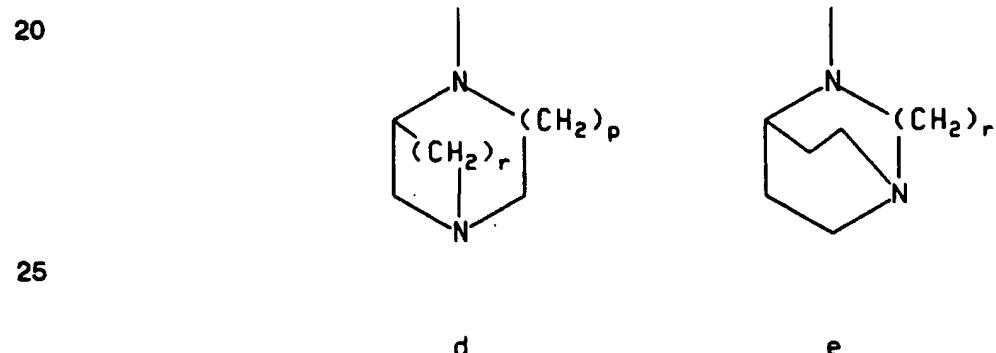
5 azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl,  $(C_1-C_6)$ acylpiperazinyl,  $(C_1-C_6)$ alkylpiperazinyl,  $(C_6-C_{10})$ arylpiperazinyl,  $(C_5-C_9)$ heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



a

b

c



d

e

wherein  $r$  is 1, 2 or 3;

30  $m$  is 1 or 2;

$p$  is 0 or 1; and

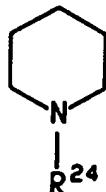
$Q$  is hydrogen,  $(C_1-C_3)$ alkyl,  $(C_1-C_6)$ acyl or  $(C_1-C_6)$ alkoxy carbamoyl;

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or R<sup>1</sup> and R<sup>2</sup>, or R<sup>3</sup> and R<sup>4</sup>, or R<sup>5</sup> and R<sup>6</sup> may be taken together to form a carbonyl;

or R<sup>1</sup> and R<sup>2</sup>, or R<sup>3</sup> and R<sup>4</sup>, or R<sup>5</sup> and R<sup>6</sup>, or R<sup>7</sup> and R<sup>8</sup> may be taken together to form a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, oxacyclohexyl, thiacyclohexyl, indanyl or tetralinyl ring or

5 a group of the formula



10

wherein R<sup>24</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)acyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>6</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl; and

Ar is (C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>5</sub>-C<sub>6</sub>)heteroaryl, each of which may be optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkyl, one or two (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy or (C<sub>5</sub>-C<sub>6</sub>)heteroaryloxy;

15 with the proviso that R<sup>7</sup> is other than hydrogen only when R<sup>8</sup> is other than hydrogen;

with the proviso that R<sup>8</sup> is other than hydrogen only when R<sup>5</sup> is other than hydrogen;

20 with the proviso that R<sup>3</sup> is other than hydrogen only when R<sup>4</sup> is other than hydrogen;

with the proviso that R<sup>2</sup> is other than hydrogen only when R<sup>1</sup> is other than hydrogen;

25 with the proviso that when R<sup>1</sup>, R<sup>2</sup> and R<sup>8</sup> are a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 2- or 6- positions;

with the proviso that when X is nitrogen, R<sup>4</sup> is not present;

with the proviso that when X is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R<sup>1</sup>, R<sup>2</sup>, R<sup>5</sup> and R<sup>8</sup>, is a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 4- or 6- positions;

30 with the proviso that when Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R<sup>3</sup>, R<sup>4</sup>, R<sup>7</sup> and R<sup>8</sup>, are independently a

substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 3- or 5- positions;

with the proviso that when X is oxygen, sulfur, sulfoxide or sulfone, R<sup>3</sup> and R<sup>4</sup> are not present;

5 with the proviso that when Y is nitrogen, R<sup>4</sup> is not present;

with the proviso that when Y is oxygen, sulfur, sulfoxide or sulfone, R<sup>5</sup> and R<sup>6</sup> are not present;

with the proviso that when Y is nitrogen, R<sup>6</sup> is not present;

10 with the proviso that when the broken line represents a double bond, R<sup>4</sup> and R<sup>6</sup> are not present;

with the proviso that when R<sup>3</sup> and R<sup>5</sup> are independently a substituent comprising a heteroatom when the broken line represents a double bond, the heteroatom cannot be directly bonded to positions X and Y;

15 with the proviso that when either the X or Y position is oxygen, sulfur, sulfoxide, sulfone or nitrogen, the other of X or Y is carbon;

with the proviso that when X or Y is defined by a heteroatom, the broken line does not represent a double bond;

20 with the proviso that when R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are all defined by hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, either X or Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen, or the broken line represents a double bond.

2. A compound according to claim 1, wherein Y is oxygen, nitrogen or sulfur.

3. A compound according to claim 1, wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

25 4. A compound according to claim 1, wherein R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

5. A compound according to claim 1, wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>9</sup> are hydrogen.

30 6. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

7. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

8. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

9. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

10. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

11. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>6</sub>-C<sub>10</sub>)arylalkynyl or (C<sub>5</sub>-C<sub>9</sub>)heteroarylalkynyl.

12. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

13. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is carboxylic acid or carboxylic acid (C<sub>1</sub>-C<sub>6</sub>)alkyl.

14. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkylamino.

15. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R<sup>8</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkylamino.

16. A compound according to claim 1, wherein said compound is selected from the group consisting of:

(2R,3S)-N-hydroxy-3-ethynyl-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(5-methoxythiophene-2-yl-ethynyl)-piperidine-2-carboxamide;

(2R,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(3-pyridin-3-yl-prop-2-ynyl)-piperidine-2-carboxamide;

(2S,3R)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-2-pyridine-3-yl-morpholine-3-carboxamide;

(2S,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-morpholine-3-carboxamide;

5 (2R,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(4-phenylpyridine-2-yl)-piperidine-2-carboxamide;

10 (2S,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-(4-phenylpyridine-2-yl)-morpholine-2-carboxamide;

(2R,3S)-N-hydroxy-3-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide; and

(2S,3R)-N-hydroxy-2-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-3-carboxamide.

15 17. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix 20 metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

18. A method for the inhibition of (a) matrix metalloproteinases or (b) the 25 production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

19. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis 30 bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to

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**said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.**

# INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/IB 95/00279

**A. CLASSIFICATION OF SUBJECT MATTER**  
**IPC 6 C07D211/96 A61K31/445 C07D241/04 C07D241/08**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**IPC 6 C07D**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP,A,0 606 046 (CIBA GEIGY AG) 13 July  1994</p> <p>see claims 1,2; example 6</p> <p>-----</p>	

Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- \*'A' document defining the general state of the art which is not considered to be of particular relevance
- \*'E' earlier document but published on or after the international filing date
- \*'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*'O' document referring to an oral disclosure, use, exhibition or other means
- \*'P' document published prior to the international filing date but later than the priority date claimed

- \*'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*'&' document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
12 December 1995	20.12.95
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/IB 95/00279

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claims 18 and 19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family membersInternal Application No  
**PCT/IB 95/00279**

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0606046	13-07-94	US-A-	5455258	03-10-95
		AU-B-	5265593	04-05-95
		CA-A-	2112779	07-07-94
		FI-A-	940012	07-07-94
		HU-A-	70536	30-10-95
		JP-A-	6256293	13-09-94
		NO-A-	940038	07-07-94
		NZ-A-	250517	26-10-95